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Acute Elevation of Blood Carboxyhemoglobin to 6% Impairs Exercise Performance and Aggravates Symptoms in Patients With Ischemic Heart Disease

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Acute exposure to carbon monoxide has the potential to impair exercise capacity in patients with ischemic heart disease. The effect of sufficient inhalation of this compound to gradually produce a level of 6% carboxyhemoglobin was studied in 30 nonsmoking patients with obstructive coronary artery disease and evidence of exercise-induced ischemia. After an initial training session, subjects were exposed to air or carbon monoxide on successive days in a randomized double-blind crossover fashion. Cardiac function and exercise capacity were assessed during symptom-limited supine radionuclide ventriculography. On the carbon monoxide day, mean postexposure carboxyhemoglobin was 5.9 ± 0.1% compared with 1.6 ± 0.1% ($p < 0.01$) after air exposure.

The mean duration of exercise was significantly longer after air compared with carbon monoxide exposure (626 ± 50 s for air versus 585 ± 49 s for carbon monoxide, $p < 0.05$). Actuarial methods suggested that subjects were likely to experience angina earlier during exercise on the day of carbon monoxide exposure ($p < 0.05$). Both the level (62 ± 2.4 versus 60 ± 2.4%, $p = 0.05$) and change in left ventricular ejection fraction at submaximal exercise (1.6 ± 1.6 versus −1.2 ± 1.6%, $p = 0.05$) were greater on the air exposure day compared with the carbon monoxide day. The peak exercise left ventricular ejection fraction was not different for the two exposures (57 ± 2.5% for both). These results demonstrate earlier onset of ventricular dysfunction, angina and poorer exercise performance in patients with ischemic heart disease after acute carbon monoxide exposure sufficient to increase blood carboxyhemoglobin to 6%.

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Inadequate coronary blood flow during stress in patients with ischemic heart disease makes optimal function of the system for delivery of oxygen to working myocardium critical. Carbon monoxide has the potential, through its high affinity for hemoglobin and influence on the oxygen dissociation curve (1), to reduce oxygen transport to cardiac muscle so that exposure to this compound could enhance myocardial ischemia during vigorous activity in patients with obstructive coronary disease. Concern has developed that such a deleterious cardiac effect might occur at the low levels of carboxyhemoglobin acquired during the course of ordinary activities in many areas of the country. Despite extensive previous investigations (2–14), controversy continues over whether these concentrations do in fact produce detectable exercise impairment in patients with ischemic heart disease.

A prior study from this laboratory (15) did not demonstrate convincing evidence of such effects at a level of 4% carboxyhemoglobin. The present study extends this work to an average post-exposure concentration of 6%. Nonsmoking

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patients with coronary artery disease and evidence of exercise-induced ischemia underwent supine bicycle exercise after double blind exposure to air or carbon monoxide in a crossover design. Comparative exercise performance after these exposures was assessed by clinical, electrocardiographic (ECG) and radionuclide variables. Subjective and objective indexes of cardiovascular function derived from these studies indicated a deleterious effect of 6% carboxyhemoglobin on patient performance.

Methods

Study patients. Patients for the study protocol were recruited from the inpatient and outpatient cardiology services of North Carolina Memorial Hospital and by advertisement in the area surrounding the University. The protocol was approved by the Institutional Review Board of the University of North Carolina. Written informed consent was obtained from all subjects before participation in the study.

Careful attention was given to the documentation of coronary artery disease and determination that a history of exercise-induced ischemia was present to select appropriate subjects for the study. Criteria for the diagnosis of coronary artery disease consisted of at least one of the following:

1) Angiographic evidence of coronary artery obstruction with at least one major vessel having ≥70% stenosis.

2) Prior myocardial infarction documented by at least two of the following three criteria: a) chest pain syndrome consistent with infarction; b) evolutionary electrocardiographic (ECG) changes; or c) significant elevations of creatine kinase-MB in serum (>2× normal).

3) History of typical angina or a positive stress test, or both.

Typical angina was defined as anterior chest, neck or left arm discomfort brought on by effort and consistently relieved within several minutes by cessation of exercise or taking sublingual nitroglycerin. For this study, a positive stress test was defined as horizontal or downsloping ST depression ≥1 mm at 0.08 s after the J point during treadmill exercise or failure of the stress ejection fraction to increase ≥5 U from the value at rest during radionuclide testing. In addition to documentation of coronary artery disease, all patients scheduled for the training day were required to have prior evidence of exercise-induced myocardial ischemia. This was manifested by a history of typical angina or a prior positive stress test as defined previously.

Patients found during screening to have valvular heart disease or major systemic illness were not studied. No patient had uncontrolled hypertension, orthopedic problems or peripheral vascular disease sufficient to prevent cardiac symptom-limited bicycle exercise. Anyone screened who had a history of smoking within the prior 2 months was excluded from study participation. No patient was found to have a pre-exposure venous carboxyhemoglobin concentration >2.5% during the study.

A total of 42 patients who satisfied the described criteria at initial screening participated in the training day of the protocol. One patient was excluded after this session because of poor venous access. Eight patients were eliminated from further study because of failure to develop chest pain consistent with angina or diagnostic ST segment depression typical of myocardial ischemia during the training exercise. Four patients without these findings were continued in the study after alteration of their anginal medication or adjustment of their training day exercise protocol; all four subsequently demonstrated evidence of exercise-induced ischemia on at least 1 exposure day and were included in the study analysis. Three patients, despite abnormalities on the training day, were later excluded for lack of exercise ischemia on any of the exposure days. *Thus, a final total of 30 patients, all of whom had evidence of exercise-induced ischemia on at least 1 exposure day, were included in the study analysis.*

Clinical patient characteristics. The analysis group consisted of 22 men and 8 women with a mean age of 58 ± 11 years. There were 10 patients who had never smoked and 20 previous smokers in this group. Duration since cessation of smoking varied from 2 months to 44 years in those with a history of cigarette use. Coronary artery disease was documented in 20 patients by ≥70% stenosis of one or more major vessels by angiography (7 with one vessel, 7 with two vessel and 6 with three vessel disease). Three of the remaining 10 patients had the combination of a positive exercise test and prior infarction and 6 had a positive exercise test and angina. Only one patient qualified on the basis of a positive treadmill test alone. The present study group did not include any subjects from the previous carbon monoxide protocol performed in this laboratory.

Antianginal medication was being taken by 25 of the 30 patients included in the analysis. This consisted of a beta-adrenergic antagonist alone in six patients, a long-acting nitrate only in one patient and a calcium channel antagonist alone in five. There were 13 patients taking both a beta-adrenergic and a calcium channel antagonist at the time of study. Throughout the exposure portion of the study, particular attention was devoted to ensuring that patients remained on the same doses of their medications and maintained precisely the same timing of these doses with relation to the exercise protocol.

Equipment. Exposure was carried out with the subject sitting in a chair in an environmentally controlled chamber measuring 8 × 8 × 7.5 feet (2.5 × 2.5 × 2.0 m) and constructed of 3/4 in. (3.5 cm) thick plexiglass. Complete air exchange occurred every 70 s in the chamber. The range of accuracy for carbon monoxide concentration in this chamber is ±5% of 100 parts/million (ppm). The exposure room temperature was controlled at 77 ± 2° with a humidity of 55 ± 5%.

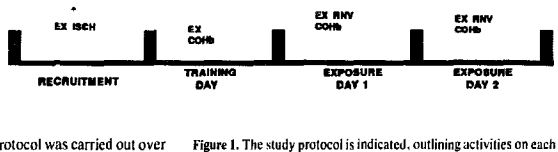


Figure 1. The study protocol is indicated, outlining activities on each of 3 consecutive study days. CAD = coronary artery disease; CO = carbon monoxide; COHb = carboxyhemoglobin; Ex = exercise; Isch = ischemia; RNV = radionuclide ventriculography.

Experimental protocol. The protocol was carried out over 3 consecutive days (Fig. 1). Day 1 was a training session during the first part of which the patient was acquainted with the protocol and allowed to sit in the exposure chamber for 10 to 20 min. A symptom-limited maximal bicycle exercise test was then performed. This test was done to minimize any training effect on subsequent exercise tests and to optimally tailor the imaging protocol performed on the following 2 days. On days 2 and 3 of the protocol, subjects were exposed to either pure air or 100 ppm (17 subjects) or 200 ppm (13 subjects) carbon monoxide in a randomized, double-blind fashion. Venous blood for carboxyhemoglobin determination was obtained before chamber entry and again after 1 h of exposure. On the carbon monoxide day, the duration of further exposure required to achieve the desired carboxyhemoglobin level of 6% was determined privately by a technician. Because the rate of increase in carboxyhemoglobin is linear in this range, the technician calculated a venous carboxyhemoglobin accumulation rate (HbCO%) for each patient as follows:

$$\frac{[1\text{ h HbCO\%}] - [\text{initial HbC\%}]}{60} = \frac{[\text{HbCO}]}{\text{min}}$$

increase. This rate of increase was used in conjunction with the rest carboxyhemoglobin level to determine the duration of additional exposure necessary to achieve 6% carboxyhemoglobin. Maintenance of double-blind conditions was accomplished by following a similar procedure on the air exposure day. During this session, the duration of additional exposure after the 1 h blood sample was determined from a set of random numbers of plausible magnitude provided to the technician by the study biostatistician.

At the appropriate time, the patients left the chamber and underwent rest and exercise radionuclide ventriculography during air breathing at a temperature of 70 ± 2°. Additional venous blood samples were taken at the time of exit from the chamber, immediately before and after exercise for determination of carboxyhemoglobin concentration.

Carboxyhemoglobin measurements. The carboxyhemoglobin levels were measured in triplicate with the use of an IL 282 Cooximeter (16). Careful standardization studies in our laboratory have demonstrated that the variance of these determinations is constant for levels in the range of 6% with an SEM of 0.15%. The technique for carboxyhemoglobin measurement employed in this study has been carefully validated against other cooximeter data, the Van Slyke technique and gas chromatography in cooperation with Dr. Thomas Dahms and co-workers at St. Louis University (personal communication).

Rest baseline carboxyhemoglobin concentration determined in nonsmoking subjects in our laboratory has a mean value of 1.7 ± 0.1% SEM. This level is relatively high compared with results of some previous studies but is within the range of nonsmoking subjects described by Stewart et al. (17). In that study, the percent of subjects with a level >1 to 1.2% varied from 18 to 76% in various parts of the United States.

Exercise protocol. All exercise tests were performed at the same time of day and in the fasting state. Stress studies were conducted in the supine position and induced by a constant load bicycle ergometer (Quinton) beginning at 0 work load for 1 min after which the work load was increased to 200 kp-m. The work load was then kept constant at this and each subsequent level for 4 min to allow time for cardiac imaging and hemodynamic equilibration. The bicycle protocol on the exposure days was designed to enable acquisition of at least one image during stress with an additional study or studies at submaximal work loads when the patient's exercise capacity permitted. The same exercise protocol was followed on each of the exposure days. At 4 min intervals, the work load was increased in 50 to 100 kp-m increments until a maximal level was achieved.

Exercise was continued until one of the following occurred: angina that required cessation of exercise, fatigue precluding further exercise, hypotension or plateau of blood pressure despite an increase in work load. Blood pressure was measured by the cuff manometric technique before, every 2 min during and each minute after exercise until stable. A 12 lead ECG was recorded immediately before and at each minute during exercise. Tracings were also obtained each minute for ≥8 min after exercise and leads II, V_4, and V_5 were continuously monitored during the study. Chest pain was graded on a scale of 1 to 10, with 10 being the

maximal pain previously experienced by the subject. A timer was used to initiate the protocol and patients were instructed to immediately inform the investigators of the onset and resolution of chest pain. These times were recorded and used to calculate onset and duration of angina in seconds. The same observers measured blood pressure and recorded the timing of symptoms on both exposure days.

Cardiac imaging. Rest and exercise equilibrium radionuclide ventriculography was performed with a large field of view gamma camera (Elscint Apex 415) fitted with a general purpose collimator. Images were acquired in the supine position from the modified left anterior oblique projection with the degree of angulation and caudal tilt selected to optimally isolate the left ventricle (18,19). A stable blood pool label was created by intravenous administration of 2 to 3 ml of unlabeled stannous pyrophosphate into a peripheral vein followed in 20 min by injection of 20 to 30 mCi of technetium-99m pertechnetate. Imaging was continued at rest until approximately 7.5 million counts were obtained. Exercise imaging began 1 min into each stage and lasted for the remainder of that stage. All radionuclide data were stored on disk for subsequent analysis with previously validated software provided by Elscint. Left ventricular ejection fraction was calculated from the image data with the use of a semiautomated region of interest program and periventricular background subtraction method (18,19).

Statistical considerations. The research design for this study had a crossover structure with separate randomization schedules for patients who were on medication and for those who were not. These schedules were balanced so that four patients in each successive set of eight received air exposure before carbon monoxide exposure and the remaining four in the reverse order. Among the 30 patients included in the study analysis, 14 underwent air exposure before carbon monoxide exposure and 16 received carbon monoxide exposure before air exposure.

The sample size of 30 patients was specified at the beginning of the study. For a previous crossover study (15) in our laboratory, the inclusion of 30 patients provided >0.90 statistical power for the comparison between air exposure and carbon monoxide exposure at 4% carboxyhemoglobin with respect to the change between rest and maximal ejection fraction. A difference between exposures of ≥5 U change in ejection fraction was used there as the target for the detection of significance with two-sided $p \leq 0.05$. Similar statistical power properties apply to the current study through its inclusion of 30 patients.

Data analysis. The following variables were analyzed to compare the air and carbon monoxide exposure days with respect to patient experiences at rest and during exercise: 1) heart rate; 2) systolic blood pressure; 3) heart rate × systolic blood pressure; 4) ECG-ST segment depression; 5) peak exercise work load; 6) exercise duration; 7) time to onset of angina pectoris; 8) duration of angina pectoris; 9) venous carboxyhemoglobin level; and 10) left ventricular ejection fraction.

For descriptive purposes, the data for the respective variables were summarized in terms of mean values and their corresponding SE for the air exposure, the carbon monoxide exposure and the difference between them. Statistical comparisons between the two exposure conditions were undertaken primarily with the Wilcoxon signed rank statistic (20) because of its applicability under minimal assumptions; paired t tests were also determined. The appropriateness of these methods was supported by the confirmation that day effects and (exposure × day) carryover effects were relatively minimal on the basis of the appropriate nonparametric procedures (21).

Some further statistical attention was given to time to onset of angina pectoris because four patients developed angina only on the carbon monoxide day. The experience of these patients for not developing angina on the air day was taken into account with an actuarial method (22). More specifically, the information concerning time to angina for each exposure was summarized in terms of the ratio for the number of patients developing angina divided by the sum of the durations of exercise for all patients; i.e., the measure reflects the number of incidents of angina per minute of exercise time and thereby represents an incidence density rate (23). The comparison of the incidence density rates for the two exposures was based on assessing the difference between their logarithms relative to its SE (that is, through the logarithm of the incidence density ratio).

The analysis of exercise ejection fraction measurements was undertaken in ways that appropriately accounted for the complex aspects of imaging requirements and differences in exercise duration on the study days. These factors created discrepancies in 10 of the 30 study patients between the 2 exposure days in the timing of final ejection fraction measurement and maximal exercise. On the basis of these considerations, two analyses of peak exercise ejection fraction were performed. The first analysis contrasted this radionuclide variable on the 2 exposure days at the final work loads regardless of whether or not they were matched. A second comparison of maximal ejection fraction was made in the 24 patients with this measurement at the same peak work load on both days.

Analysis of submaximal ejection fraction data was performed in 19 patients with more than one such measurement on ≥1 exposure day. In 13 patients, these data were available at submaximal exercise and matched work loads on both exposure days. Because of differences in exercise duration, the submaximal ejection fraction data did not correspond to submaximal exercise in both air and carbon monoxide sessions in six subjects.

Table 1. Individual Patient Data (n = 30) for Selected Exercise Measurements on the Air and Carbon Monoxide Exposure Days

Subject	Extent CAD	Time to Onset of Angina(s)		Duration of Exercise(s)		Time to Significant ST Depression(s)	
		Air	CO	Air	CO	Air	CO
1	—	—	—	270	285	—	—
2	—	267	105	370	300	—	—
3	2	200	175	325	300	240	180
4	2	180	190	280	280	120	120
5	2	80	40	220	220	—	—
6	—	—	190	406	370	240	180
7	—	—	615	795	720	360	300
8	1	130	120	540	480	250	360
9	3	—	—	345	320	240	300
10	—	585	505	1,020	1,020	360	420
11	3	150	190	540	540	—	—
12	2	625	600	1,280	1,170	—	—
13	3	120	150	180	180	120	120
14	—	360	325	720	490	480	480
15	1	370	255	740	720	—	—
16	1	—	—	780	780	—	600
17	—	—	780	780	780	660	300
18	2	580	345	780	780	—	660
19	3	228	230	868	840	600	660
20	1	168	130	505	330	122	120
21	2	125	200	510	550	480	—
22	—	277	335	1,020	780	180	240
23	3	510	255	540	360	395	240
24	3	245	142	510	332	360	120
25	2	252	350	614	750	300	122
26	—	—	—	840	840	540	840
27	1	—	870	1,020	1,020	783	720
28	—	—	—	720	759	363	360
29	1	239	225	462	540	180	240
30	1	348	623	798	720	300	240

CO = carbon monoxide. Extent CAD = number of major epicardial coronary arteries with at least one stenosis ≥70%.

Results

Carboxyhemoglobin levels. The mean rest carboxyhemoglobin level was 1.7 ± 0.1% on the carbon monoxide day and slightly higher 1.9 ± 0.1% on the air day ($p < 0.01$). The mean level obtained immediately after carbon monoxide exposure was 5.9 ± 0.1% and fell to 5.2 ± 0.1% after exercise in room air. (The mean difference between carboxyhemoglobin during exercise testing on the carbon monoxide exposure day versus air exposure day was about 4.0% [5.6 to 1.6%].) On the air day the carboxyhemoglobin concentration dropped from 1.9 ± 0.1 to 1.6 ± 0.1% during chamber exposure ($p < 0.01$) and was 1.6 ± 0.1% after exercise.

Exercise-induced ischemia (Table 1). All 30 patients included in the study analysis had evidence of ischemia during exercise on at least one of the exposure days as manifested by ST segment criteria (≥1 mm horizontal or downsloping ST depression in 24 of 30), typical angina during exercise (25 of 30) or an abnormal exercise ejection fraction response (failure to increase ≥5 U from rest in 26 of 30).

Air exposure day. Rest left ventricular ejection fraction was in the normal range (≥53%) in 20 of the 30 patients on the air day and no patient had a value of <40%. Mean rest left ventricular ejection fraction was 58 ± 1.7% on the day of air exposure and essentially did not change at peak exercise. For 22 of the 30 patients, the change in ejection fraction from rest to maximal exercise was <5 U on the air day. Chest pain consistent with angina developed in 21 of the 30 patients on the air day. Time to onset of angina averaged 288 ± 36 s for these 21 patients and chest pain was prolonged with a mean duration of 484 ± 46 s. Mean maximal ST segment depression was 1.6 ± 0.2 mm on the air day for the 22 patients showing ≥1 mm of ST depression.

Exercise air versus carbon monoxide exposure. There was no significant difference in rest heart rate between the

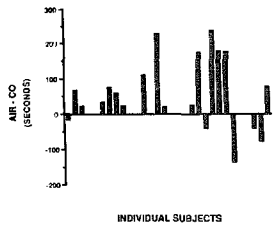


Figure 2. Study data showing the difference in exercise duration between the air and the carbon monoxide (CO) exposure day on the Y axis and 30 individual subjects on the X axis. In 10 subjects there was no change in exercise duration between the study days.

exposure days (60 ± 1.8 beats/min for air versus 60 ± 1.8 beats/min for carbon monoxide). Rest blood pressure was slightly higher after air as compared with carbon monoxide exposure (157 ± 4.2 mm Hg for air versus 152 ± 4.0 mm Hg for carbon monoxide, $p < 0.05$). The mean duration of exercise was significantly longer after air exposure (626 ± 50 s for air versus 585 ± 49 s for carbon monoxide, $p = 0.02$). Only 5 of the 30 patients had longer exercise duration after carbon monoxide compared with air exposure (Fig. 2). In 15 patients, exercise lasted longer on the air day and for 10 of these patients, it was at least 1 min longer. There was a difference in exercise duration of 69 ± 35 s in favor of the air day among the six study patients with three vessel disease.

Time to onset of angina was greater on the air day in 13 of 21 patients with this finding on both exposure days. This difference exceeded 1 min in 6 of the 13. There was a suggestive tendency for onset of angina to occur earlier on the carbon monoxide day in the 21 subjects with this symptom on both exposure days (288 ± 36 s for air versus 261 ± 34 s for carbon monoxide, $p = 0.25$). The difference in time to onset of angina between the air and carbon monoxide days in the five study patients with three vessel disease and this symptom on both days was 57 ± 56 s. In four patients, angina developed during exercise only on the day of carbon monoxide exposure; no patient had this symptom on the air day alone. An actuarial method (22) directed at the ratio of the proportion of patients with angina divided by the average duration of exercise indicated that the patients were likely to experience angina earlier during stress on the carbon monoxide day ($p < 0.05$). There was no difference between the study day in duration of angina (484 ± 46 s for air versus 438 ± 45 s for carbon monoxide for subjects with angina). Also, maximal ST segment depression (1.6 ± 0.2 mm for air versus 1.7 ± 0.2 mm for carbon monoxide for patients showing ≥1 mm of ST depression) and time to significant ST segment depression (≥1 mm) (349 ± 39 s for air versus 344 ± 45 s for carbon monoxide) were similar for the two exposures.

Maximal blood pressure achieved during exercise did not differ by exposure (192 ± 4.6 mm Hg for air versus 189 ± 5.1 mm Hg for carbon monoxide). There was a trend for maximal heart rate to be higher after carbon monoxide (105 ± 3.7 beats/min for air versus 108 ± 3.5 beats/min for carbon monoxide, $p = 0.06$); but maximal rate-pressure product (20,389 ± 1,080 for air versus 20,515 ± 1,039 for carbon monoxide) and peak work load (312 ± 28 versus 303 ± 26 kp-m) were indistinguishable on the 2 exposure days.

Radionuclide ventriculography on air versus carbon monoxide (Tables 2 and 3). Analysis of the radionuclide data (Fig. 3) revealed no significant difference in rest post-exposure left ventricular ejection fraction on the air and carbon monoxide days (58 ± 1.7 versus 58 ± 1.7, respectively). In the 19 patients with data available, the level of submaximal ejection fraction was significantly higher after air compared with carbon monoxide exposure (62 ± 2.4 versus 60 ± 2.4%, respectively, $p = 0.05$). There was also a significant difference in the change from rest to submaximal ejection fraction between the 2 exposure days (1.6 ± 1.6% for air versus −1.2 ± 1.6% for carbon monoxide, $p = 0.05$).

There was no difference in maximal ejection fraction after air and carbon monoxide exposure among the 30 subjects with these data available at matched or unmatched work loads on the study days (57 ± 2.2% for air versus 57 ± 2.1% for carbon monoxide). No difference in peak ejection fraction was found among the 24 patients with this measurement at similar work loads on the 2 exposure days (57 ± 2.5% for air versus 57 ± 2.5% for carbon monoxide). The difference in change in peak ejection fraction between the air and carbon monoxide days was 5.4 ± 3.0% for the 5 of these 24 study patients with three vessel disease.

Impaired exercise performance on carbon monoxide exposure. The study data reported here are the first to demonstrate impairment of exercise ventricular function due to low level exposure to carbon monoxide in patients with ischemic heart disease. Left ventricular performance, as assessed by radionuclide ejection fraction measurement, was reduced during exercise after exposure to carbon monoxide compared with air. In addition, other measurements indicated that inhalation of this compound sufficient to produce a 6% carboxyhemoglobin plasma level was associated with a reduction in exercise performance and aggravation of symptoms. Exercise duration was significantly shorter after carbon monoxide than after air exposure. There was a trend for an earlier onset of angina after inhalation of this compound among patients with this symptom on both exposure days. Analysis by actuarial methods demonstrated that the timing of this end point occurred earlier during exercise after carbon monoxide exposure compared with air exposure.

Although the changes we observed in exercise performance between the air and carbon monoxide days were

Table 2. Individual Patient Data (n = 30) for Selected Radionuclide Measurements on the Air and Carbon Monoxide Exposure Days

		LVE at Rest		Submaximal LVEF		Maximal LVEF	
Subject	Subset	Air	CO	Air	CO	Air	CO
1	C	71	66	—	—	70	73
2	C	49	46	—	—	53*	46
3	C	41	45	—	—	36	40
4	C	62	62	—	—	63	66
5	C	40	39	—	—	42	44
6	A	72	76	71	66	58	66
7	A	56	60	54	59	52	62
8	A	59	65	67	69	71	70
9	C	59	56	—	—	60	59
10	A	57	50	66	52	67	57
11	A	48	52	54	52	53	55
12	B	48	53	64	58	57	—
13	C	47	49	—	—	39	30
14	B	64	63	68	67	76	—
15	C	42	42	42	—	39	45
16	A	63	61	62	58	57	50
17	A	65	58	66	57	60	60
18	B	60	57	56	54	52	—
19	A	49	50	53	47	52	51
20	C	56	55	—	—	49*	44
21	C	53	53	—	54	59	54
22	B	61	67	48	47	51	—
23	B	62	69	63	59	65	—
24	C	60	73	—	—	65*	64
25	B	60	51	49	49	—	55
26	A	70	68	75	75	74*	72*
27	A	76	77	86	87	86	82
28	A	50	56	54	55	50	57
29	A	55	54	48	52	45	51
30	A	72	70	73	72	69	70

*Maximal LVEF not taken at peak work load. Subsets have the following definitions: subset A consists of 13 patients with both submaximal and maximal exercise at matched work loads; subset B consists of six patients with submaximal exercise at matched work loads on both exposure days but with a corresponding maximal exercise missing for one exposure; subset C consists of 11 patients with maximal exercise at matched work loads but with submaximal exercise missing. CO = carbon monoxide; LVEF = left ventricular ejection fraction.

significant, in the group as a whole they were not severe. Peak left ventricular ejection fraction was unaltered and the mean difference in exercise duration was <1 min. This finding suggests that a 6% carboxyhemoglobin level is near the threshold necessary for adverse effects on exercise performance from an acute exposure to carbon monoxide among a broad group of patients with ischemic heart disease. It is important to note that deleterious effects of this exposure level were more pronounced in individual patients and especially in the small cohort of patients with three vessel coronary disease.

Enhanced hypoxia. These subjective and objective indexes of exercise performance suggest that a 6% blood carboxyhemoglobin level is sufficient to impair exercise myocardial oxygenation in ischemic heart disease. Total duration of exercise has been related by the present investigators (24) and others (25,26) to the development and magnitude of exercise-induced myocardial ischemia. Early radionuclide studies (27,28) linked left ventricular ejection fraction response during exercise to the presence or absence of myocardial ischemia (27,28). Since subsequent investigation had demonstrated that functional response is not entirely a reflection of ischemia, we carefully considered other factors that could have influenced our exercise ejection fraction results. Primary myocardial and valvular heart disease alone may produce exercise left ventricular dysfunction (29,30), so patients with these disorders were excluded from the protocol. Patients with coronary artery disease and marked rest cardiac dysfunction may have a poor ventricular response to exercise even in the absence of ischemia (31,32).

Table 3. Mean Radionuclide Data: Air Versus Carbon Monoxide

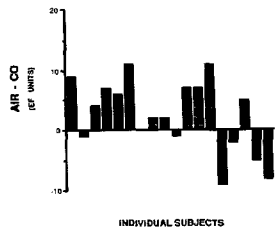
Variable	Air	CO	Diff	n for Diff	p Value for Diff
Rest LVEF	58 ± 1.7	58 ± 1.7	0.9 ± 0.9	30	0.30
Submaximal LVEF	62 ± 2.4	60 ± 2.4	2.2 ± 1.0	19	0.05
Maximal LVEF	57 ± 2.5	57 ± 2.5	0.0 ± 1.1	24	0.99
Submaximal ΔLVEF	1.6 ± 1.6	1.2 ± 1.6	2.7 ± 1.2	19	0.05
Maximal ΔLVEF	0.1 ± 1.4	−1.0 ± 1.4	0.9 ± 1.2	24	0.58

Results are shown as mean ± SEM. Diff = (Air − CO) difference; other abbreviations as in Table 2. p value based on Wilcoxon signed rank statistics.

However, the subjects we studied had a mean rest ejection fraction within the normal range. Although female gender may be associated with poor ejection fraction response to exercise (33), the majority of the present study patients were male. Finally, the present study design compared exercise ejection fraction response after air and carbon monoxide exposure in the same subject. The work of Hecht et al. (34) suggests that if paired exercise radionuclide ventriculograms are obtained in a group of patients under similar clinical conditions, any differences in response between the two sessions should be minor and statistically insignificant.

These considerations suggest that the greater exercise myocardial dysfunction after carbon monoxide was due to a toxic effect of this compound on cardiac oxygenation. This result is consistent with the substantial impact on tissue oxygen delivery that occurs from relatively small elevations in carboxyhemohoxyhemoglobin concentration (1,4). The high affinity of hemoglobin for carbon monoxide directly reduces oxygen carrying capacity by displacing bound oxygen. At the tissue level, a more profound effect, greater than that expected from direct displacement occurs, owing to the increase in affinity of hemoglobin for the oxygen that remains.

Figure 3. Study data showing the difference in ejection fraction (EF) response at submaximal exercise between the air and carbon monoxide days on the Y axis and 19 individual subjects on the X axis. Abbreviations as in Figure 2. Two subjects had no difference in submaximal ejection fraction response on the two study days.



Potential limitations of the study. Our results did not support a deleterious influence of this blood level of carboxyhemoglobin on maximal exercise left ventricular function. Several factors related to the study design and the constraints of the imaging protocol likely contributed to this finding. Differences in exercise duration that could have independently influenced peak function prevented comparison of maximal ejection fraction on the air and carbon monoxide days in 10 patients. Restriction of the analysis to the 20 patients whose peak work load and ejection fraction data coincided on the 2 exposure days was not possible. Use of these subjects alone would have introduced a bias because requiring identical periods of exercise on both days selects a group that may have had less carbon monoxide effect. Because equilibrium imaging requires several minutes for data acquisition, it is also possible that differences in ventricular function occurring toward the end of exercise could have been missed.

Finally, we investigated a broad spectrum of patients with coronary artery disease at target blood levels of carboxyhemoglobin expected to be close to threshold for cardiovascular effects. In this setting, it is unclear whether functional differences would be seen at both maximal and submaximal exercise. Our study does not rule out the potential of greater peak exercise dysfunction after carbon monoxide compared with air exposure at higher levels of carboxyhemoglobin or in patients with more severe ischemic heart disease. Although only suggestive because of the small numbers involved, our study data in patients with three vessel coronary disease were consistent with this latter possibility.

The great majority of patients were taking antianginal medications at the time of study. Although these drugs had the potential to mask the effects of carbon monoxide exposure, such masking did not occur. Further, the inclusion of patients on such medication improves our understanding of the impact of carbon monoxide exposure in the broad range of patients with ischemic heart disease. Our data cannot, however, rule out the possibility that even greater impair-

ment of exercise performance might have occurred at this level of carboxyhemoglobin in patients not taking medications to control angina.

Smokers were excluded from the present investigations so that the specific effect of carbon monoxide inhalation could be studied. Recent data (35) indicate that nicotine may act as a direct coronary vasoconstrictor and produce myocardial ischemia. Thus, active or passive smoking sufficient to produce the same level of carboxyhemoglobin attained in this study may be associated with greater impairment of exercise performance.

The present study group was biased toward patients with the symptom of angina, this end point being found in 25 patients during the course of the study. Recent investigation (36) has documented the common occurrence of transient episodes of myocardial ischemia without associated chest pain. The physiologic effects of carbon monoxide exposure in patients with predominantly silent or with mixed symptomatic and silent ischemia are not addressed by the present work.

Previous studies. Our studies represent the largest patient experience concerning the toxic effects of carbon monoxide on exercise performance in ischemic heart disease. This work suggests that the threshold for an adverse effect of blood carboxyhemoglobin on exercise performance in general populations of patients with ischemic heart disease is between 4 and 6%. Our studies differ in design and results when compared with much previous work on the adverse effects of acute elevation of this compound in coronary artery disease. Aronow and Rokaw (7) studied the influence of carbon monoxide exposure sufficient to attain 7.8% carboxyhemoglobin on exercise performance in 10 patients with ischemic disease. Although the exposure sequence was randomized, the study was not blinded. The protocol design included smokers with only a 12 h interval between the protocol and cessation of smoking. The unblinded nature of the study and the inclusion of smokers could have independently influenced the observed association between exercise performance and carbon monoxide inhalation. Aronow and Isbell (8) studied the toxicity of carbon monoxide in 10 patients with angina with a blinded study design. Although no patient was a current smoker, the time between cessation of cigarette use and performance of the protocol was not given. The patients had undergone a minimum of 10 previous exercise tests and they had a consistent time to onset of chest pain. Anderson et al. (13) reported an adverse effect of low level carbon monoxide exposure in patients with ischemic heart disease. Their small study population of 10 patients included smokers and utilized a somewhat unorthodox exposure protocol allowing "rest" periods interspersed with exposure to gases through a mask. The study methods suggest that the subjects were not taking anti-anginal medications during the protocol period. Such design differences could have contributed to the disparities between these latter two studies and the work from our laboratory. In 1981, Aronow (14) reported an adverse effect of 2% carboxyhemoglobin on exercise performance in 15 patients with angina. In contrast to studies from our laboratory, only 8 of the subjects had evidence of ST depression during exercise to corroborate the ischemic origin of their chest pain.

None of the previous studies of which we are aware have included measurement of ventricular function to validate the ischemic nature of the subjective end point of time to onset of chest pain. The studies conducted by our group have incorporated stringent design features including the use of an exposure chamber to enhance the double blind nature of the sessions. Our studies have involved a wide cross section of patients with ischemic heart disease rather than being restricted to those with reproducible exercise-induced chest pain. We have included patients taking anti-anginal medications and with varying severity of underlying coronary artery disease. These additional factors likely contribute to the difference in the threshold for carbon monoxide toxicity suggested by the present and prior work.

Health effects. The issue of cardiac toxicity related to the inhalation of carbon monoxide remains of interest despite current regulations designed to limit environmental exposure to this compound. The population at risk is large; there are estimated to be 2 million patients with coronary artery disease complicated by angina in the United States today (37) who would be at risk from carbon monoxide exposure. Recent reports (31) do document a fall in the average ambient carbon monoxide level in most urban areas from 1977 to 1986 (38). In sites that conform to the national air quality standard of an average of <9 ppm carbon monoxide for an 8 h period or <35 ppm for a 1 h period, achievement of carboxyhemoglobin levels similar to those examined in this study would be unlikely. However, in a number of specific environmental situations such as tunnels, houses with defective gas furnaces and closed automobiles during heavy freeway traffic, it would be possible to achieve the levels of carboxyhemoglobin investigated here. In addition, patients at risk who continue to smoke often experience levels of at least the magnitude investigated in the present study (39). The available data suggest that despite long-term exposure, deleterious effects of acute carbon monoxide exposure persist in those who use cigarettes.

Conclusions. The study results reported here indicate that acute exposure to carbon monoxide sufficient to produce a plasma carboxyhemoglobin level of 6% is associated with significant impairment of exercise performance in patients with ischemic heart disease. The difference in ventricular performance observed after carbon monoxide compared with air exposure provides the first description of a direct toxic effect of this compound on exercise ventricular function. The most likely explanation for these deleterious effects of carbon monoxide is a worsening of myocardial ischemia due to impaired oxygen delivery to working myocardium.

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